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Metabolism and Toxicology of Pyrethroids with Dihalovinyl Substituents

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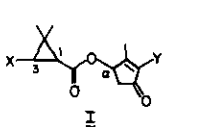
Replacement of the photolabile and biodegradable isobutenyl substituent of pyrethroids with a dihalovinyl group often leads to improved insecticidal potency and enhanced photostability. This type of structural modification does not greatly alter the ease of detoxification in mammals since other sites in the molecule undergo metabolic attack. The available toxicological information on dihalovinyl pyrethroids indicates that they are suitable replacements for other insecticides with less favorable persistence and toxicological characteristics.

Pest control to maintain and improve crop yields and human health standards requires the use of effective and biodegradable insecticides with minimal hazard for man, domestic animals and wildlife. Strong reliance was placed in the past on chlorinated hydrocarbon insecticides, such as DDT and the cyclodienes, compounds whose use is now restricted because of unfavorable persistence and toxicological properties. The current replacements for chlorinated hydrocarbons are organophosphorus compounds and methylcarbamates that are less persistent but many of which have a high acute toxicity for man and higher animals. There is a critical need for alternative insecticides with many of the benefits but not the disadvantages of the chlorinated hydrocarbons. It appears likely that some of the newer pyrethroids will meet this need.

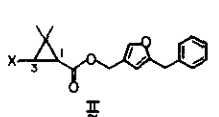
Discovery and Structure–Activity Relationships

Pyrethroids, one of the oldest classes of insecticides, have been modified in recent years to bring them to the forefront as insect control agents for agriculture and public health. Pyrethrum flowers and their extracts were used for more than a century prior to identification of the six insecticidal components, the most active of which is pyrethrin I (I) (*1*). Twenty-five years of structure–activity studies resulted in a series of useful synthetic pyrethroids, starting with allethrin and later including resmethrin and phenothrin and a variety of other chrysanthemates important in household, veterinary and stored products insect control (*2–6*). The 1R isomers are much more active than the 1S isomers, while the optimal configuration at the 3-position varies between different series of compounds.



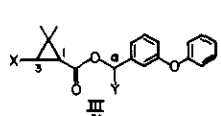
I

pyrethrin I (1R,3S,αS): X = Me_2C=CH–; Y = $-CH_2CH$=$CHCH$=CH_2
allethrin (1RS,3RS,αRS): X = Me_2C=CH–; Y = $-CH_2CH$=CH_2
"dichloroallethrin" (1RS,3RS,αRS): X = Cl_2C=CH–; Y = $-CH_2CH$=CH_2



II

resmethrin (1RS,3RS): X = Me_2C=CH–
"haloresmethrins" (various isomers): X = Cl_2C=CH– or other halogen analogs



III

phenothrin (1RS,3RS): X = Me_2C=CH–; Y = –H
permethrin (1RS,3RS): X = Cl_2C=CH–; Y = –H
NRDC 149 (1RS,3RS,αRS): X = Cl_2C=CH–; Y = –CN
decamethrin (1R,3R,αS): X = Br_2C=CH–; Y = –CN

(1)

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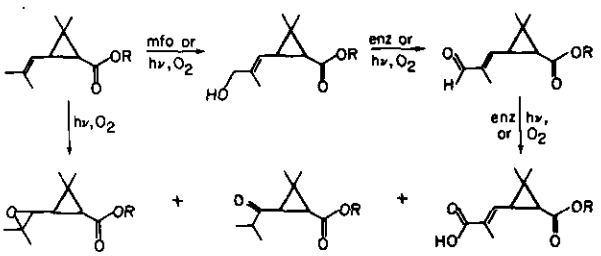
Chrysanthemates with a variety of alcohol moieties proved inefficient in crop protection, in part because they lacked sufficient stability in light and air. Attempts to stabilize them by adding antioxidants or by formulation to minimize decomposition proved inadequate. It became apparent that improved pyrethroids must combine increased potency with enhanced photostability.

The isobutenyl substituent of chrysanthemates is important in conferring high insecticidal activity but it also limits their metabolic and photochemical stability [Eq. (1)]. Insects rapidly oxidize the *trans*-methyl group of this substituent to the corresponding alcohol, aldehyde, and carboxylic acid with loss of insecticidal activity (*7, 8*). This oxidation is inhibited and the insecticidal activity increased on addition of a mixed-function oxidase (mfo) inhibitor such as piperonyl butoxide (PB). The isobutenyl group also undergoes rapid photooxidation, forming the epoxide and various hydroxy, keto, and carboxylic acid derivatives (*9–11*). Pyrethroids of greater insecticidal activity and persistence therefore require replacement of the isobutenyl group by more stable substituents which maintain adequate fit at the insect nerve receptor site.



(2)

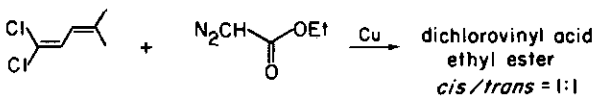
On replacement of the isobutenyl group with a dichlorovinyl substituent, the highly insecticidal allethrin is converted to "dichloroallethrin" (I) with a 3-fold increase in potency for killing houseflies and a 3-fold decrease in knockdown activity (*12*). This same type of structural modification was found many years later to increase the potency and stability of other chrysanthemate insecticides (*3–6, 13–21*) (Table 1). The dihalovinyl-containing esters of 3-phenoxybenzyl alcohol (*e.g.*, permethrin), although less potent than the corresponding esters of 5-benzyl-3-furylmethyl alcohol (i.e., the haloresmethrins), are preferred for two reasons: they are more stable in light and air since they lack the photolabile furan group; they are less toxic to mammals (*6, 9, 13–15, 17, 18*). Incorporation of an α-cyano group further increases the potency of the phenoxybenzyl esters (*3–6, 16, 18, 22, 23*). Particularly active compounds are NRDC 149 and decamethrin. The αS configuration at the benzyl carbon provides much greater potency than its αR isomer (*16*). Decamethrin, the 1R-ester with a 3R-dibromovinyl substituent and an αS-cyano group, is the most potent insecticide known of any type (*16*).

The dihalovinyl pyrethroids are more expensive than most other insecticides. Fortunately, these pyrethroids are effective at very low doses (10–100 gr/ha depending on the compound and the pest) and they are sufficiently stable that one or only a few applications per season may suffice. The potency of these pyrethroids has other beneficial aspects in that the very low dose required minimizes crop residues and the environmental burden in agricultural areas. Further, there are higher crop yields in some cases due to reduced phytotoxicity relative to other insecticides.

Synthesis

3-(2,2-Dihalovinyl)-2,2-dimethylcyclopropanecarboxylic acids, the acid moieties of dihalovinyl pyrethroids, can be prepared by several routes involving a variety of starting materials and yielding products with different *cis/trans* isomer ratios or stereochemical purities. A few examples are given below, using the dichlorovinyl acid for illustration.

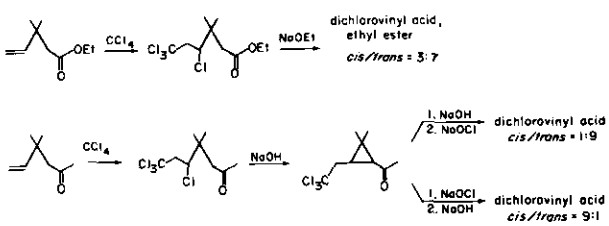
The ethyl ester of the dichlorovinyl acid was first prepared by the carbene reaction of ethyl diazoacetate and 1,1-dichloro-4-methyl-1,3-pentadiene [Eq. (2)] (*12*).



(3)

Many methods are currently being evaluated for commercial synthesis of the dichlorodiene (*12, 24, 25*). This route to the dichlorovinyl ester requires special precautions in the safe handling of ethyl diazoacetate.

The dichlorovinyl acid or its esters can also be prepared by radical addition of carbon tetrachloride to appropriate unsaturated esters (*26*) or ketones (*27*) [Eqs. (3) and (4)].



(4)

Table 1. Influence of 3-(2,2-dihalovinyl) replacement for 3-isobutenyl substituent on toxicity and biodegradability of 2,2-dimethylcyclopropanecarboxylates of 5-benzyl-3-furylmethanol, 3-phenoxybenzyl alcohol and α-cyano-3-phenoxybenzyl alcohol.

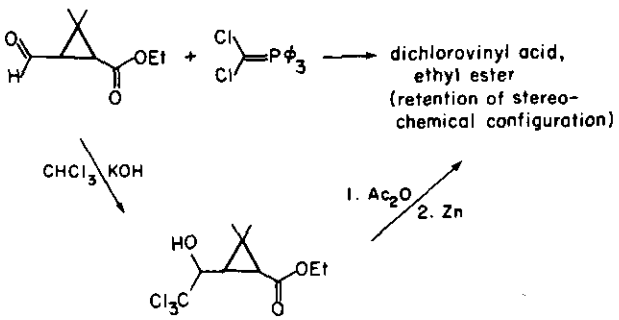
Compound	X group of 3-substituent, $X_2C=CH-$	Stereochemistry 1	3	α	Insecticidal potency relative to [1R,3S]-resmethrin[a] Housefly topical	Mustard beetle topical	Mouse intraperitoneal LD_{50}, mg/kg[b] Alone	+DEF	+PB	Mouse microsomal metabolism rate relative to [1R,3S]-resmethrin[c] Esterase	Oxidase	Esterase + oxidase
5-Benzyl-3-furylmethyl	Me	R	S	—	100	100	>1500	>1500	>1500	79	20	100
2,2-dimethylcyclopro-		R	R	—	41	30	320	29	13	<3	29	29
panecarboxylates (II)	F	R	S	—	390	180				143	8	181
		R	R	—	260	200				<4	10	13
	Cl	R	S	—	350	320				155	21	180
		R	R	—	280	290				<2	24	27
	Br	R	S	—	210	270				61[d]	15[d]	84[d]
		R	R	—	360	250						
3-Phenoxybenzyl	Me	R	S	—	53	45	>1500	>1500	>1500	59	27	78
2,2-dimethylcyclopro-		R	R	—	46	16	>1500	>1500	>1500	<4	37	37
panecarboxylates (III, Y=H)	F	R	S	—	61	46						
		R	R	—	170	120						
	Cl	R	S	—	90	260	>1000[f]	>1000[f]	>1000[f]	77	30	112
		R	R	—	200	160	1000[f]			<2	26	29
	Br	R	S	—	110	94				20	15	36
		R	R	—	260	200				<2	18	19
α-Cyano-3-phenoxybenzyl	Me	R	S	RS	150	90	>500	25	25	3	5	11
2,2-dimethylcyclopro-		R	R	RS			58	19	8	<3	8	12
panecarboxylates (III, Y=CN)	F	R	S	RS	94	84						
		R	R	RS	150	270						
	Cl	R	S	RS	570	320	>500[f]	25[f]	50[f]	17[d]	4[d]	18[d]
		R	R	RS	1300	1000	28[e]	6[e]	5[e]	<2[e]	5[e]	7[e]
	Br	R	S	RS	550	410	>500	25	450			
		R	R	RS	1200	1300	22	9.5	6.0			
		R	R	S	2300	1600	10	5.0	2.9	<3	<4	<4

[a]See references (*3*, *16-18*).
[b]See references (*34*, *42*).
[c]See reference (*41*).
[d]1RS, *trans* isomer.
[e]1RS, *cis* isomer.

Synthesis via the ester generally gives more *trans* than *cis* isomer, whereas the ketone intermediate yields either *trans*-rich or *cis*-rich mixtures, depending on the order of treatment with base and oxidant.

In some cases it is advantageous to use a specific stereoisomer (1R,3S or 1R,3R) of the acid in preparing the pyrethroid. The *cis*- and *trans*-isomers as their ethyl esters are readily separated by spinning band distillation and the 1R and 1S epimers of the *cis*- or *trans*-acid are easily resolved with appropriate optically active amines (*17*). The 1S isomer of the dichlorovinyl acid chloride can be thermally epimerized to its 1R isomer (*28*).

The 1R,3S isomer of chrysanthemic acid is obtained in a somewhat analogous manner (*29*) in the production of commercial chrysanthemate insecticides. Insecticidally inactive 1S acids can then be epimerized to the 1R acids, via their esters or chlorides (*29*), so [1R,3S]- and [1R,3R]-chrysanthemic acids are potentially available in large amounts. This is important because the chrysanthemates can be converted to the corresponding dichlorovinyl derivatives having the same stereochemistry as the starting material. Thus, ozonolysis of the chrysanthemate ester gives the caronaldehyde ester (*29*) which by a Wittig reaction (*13, 18–20*) or base addition of chloroform (*27*) gives the dichlorovinyl ester [Eq. (5)].

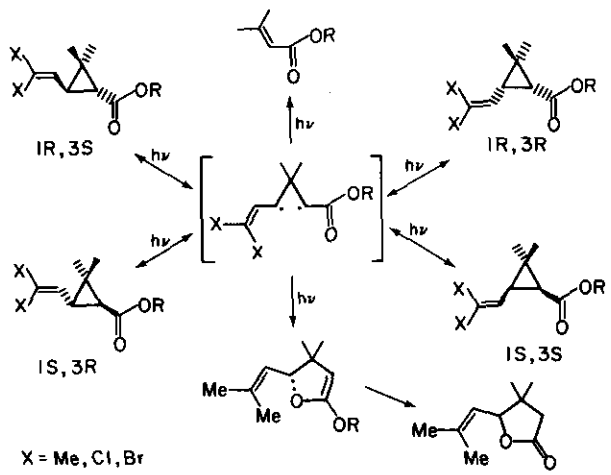


(5)

Each of these synthetic methods and others still under investigation yield their own complement of impurities, often in trace amounts, which must be considered in toxicological evaluations.

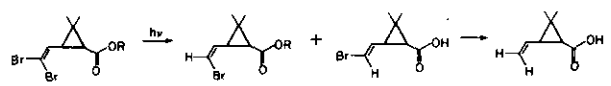
Photochemistry

Chrysanthemates and the analogous dihalovinyl compounds undergo photoisomerization via a diradical intermediate so that an individual isomer yields a 1RS,3RS mixture (*11*) with the anticipated changes in biological activity [Eqs. (6)]. This isomerization was first noted with chrysanthemates (*30–32*) and later with dihalovinyl-cyclopropanecarboxylates (*11, 33, 34*) exposed in various solvents to ultraviolet irradiation. It also occurs with dihalovinyl pyrethroids exposed to sunlight as thin films on various surfaces (*11*) and on plant foliage (*35*), where it is a relatively slow process so that the applied isomer dominates the residue picture. This *cis/trans* isomerization in solution is greatly enhanced by triplet sensitizers such as benzophenone and isobutyrophenone (*31, 33, 34*). In addition to isomerization, the 1,3-diradical intermediate can either disproportionate to yield the 3,3-dimethylacrylate (*30, 32, 34*) or cyclize after radical rearrangement to give the lactone (*30, 32*).



(6)

Reductive photodehalogenation occurs with permethrin and particularly decamethrin in solutions exposed to ultraviolet irradiation (*11, 33, 34*) but the dehalogenation products are not detected in significant amounts with either compound upon sunlight irradiation (*11, 34*).

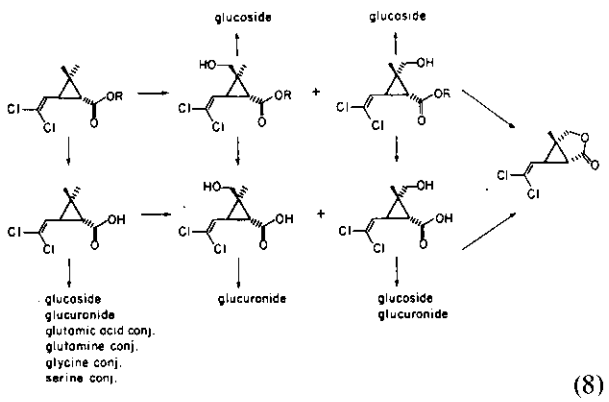


(7)

In addition to these photochemical reactions of the acid moiety, pyrethroids in general undergo modifications in the alcohol moiety and extensive ester cleavage on irradiation in solution or as thin films (*9–11, 33, 34*). Photodecomposition generally reduces the toxicity of pyrethroids (*9, 10, 34*) except in mouse assays on the resmethrin photoproducts (*9*).

Metabolism

Pyrethroids with dihalovinyl substituents are metabolized in the animal and plant systems examined by reactions that involve no modification of the dihalovinyl group. Other portions of the molecule and particularly the ester linkage and alcohol moiety are more susceptible to attack. The acid moiety of permethrin is metabolized in rats, cows, adults cockroaches, adult houseflies, cabbage looper larvae, and bean and cotton plants as shown in Eqs. (8) (*28, 35–38*). The *cis* isomer is generally cleaved more slowly than the *trans* isomer and a greater extent of oxidation of the geminal-dimethyl group is obtained with *cis*-permethrin.

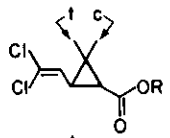
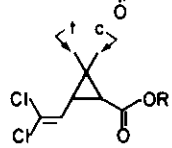


(8)

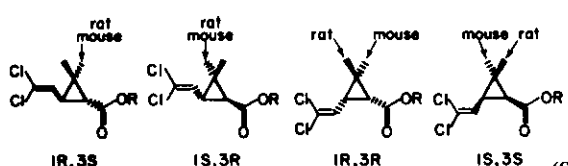
The 2-*cis*-hydroxymethyl acids and esters either undergo lactonization *in vivo* or the lactone is formed as an artifact during analysis. The type of conjugate formed is dependent on the particular organism involved. The preferred methyl group for *in vivo* hydroxylation of *trans*- and *cis*-permethrin varies somewhat with the isomer and species under investigation (*28, 35–37*). The acid moiety from decamethrin metabolism is excreted by rats as the free acid and its glucuronide and glycine conjugates, and little or no metabolites are detected which may arise by hydroxylation of the geminal-dimethyl substituent (*39*).

Microsomal enzyme systems from mouse and rat liver have been used to examine the effect of the dihalovinyl group on metabolism of pyrethroids (*40–45*). Quantitative data on mouse microsomal esterases, oxidases, and esterases plus oxidases are given in Table 1 (*41, 42*). The *cis* isomers are not cleaved at a significant rate by esterases, but they are oxidized at nearly the same rates as the corresponding *trans*-esters. Esterase cleavage is enhanced by chloro and fluoro substituents and retarded by bromo substituents. Oxidation rates are altered very little on replacing the methyl groups by chlorines but they are possibly lowered by bromo

Table 2. ***In vivo*** **metabolism of isomer mixtures.**

	Mammals		Insects		
	Rat	Cow	Cockroach	Housefly	Cabbage Looper
	*c* > *t*	*t* >> *c*	*t*	*t*	*t*
	*t* > *c*	*t*	*t* > *c*	*t* > *c*	*t*

substituents and are definitely reduced by fluoro substituents. Thus, replacement of the isobutenyl substituent, which is easily oxidized, by a dihalovinyl group does not greatly alter the overall rate of pyrethroid metabolism, presumably because other substituents are also available for oxidation, i.e., the 2′ -, 6- and especially the 4′-positions of the phenoxybenzyl moiety. In the absence of the isobutenyl group, oxidation in the acid moiety is diverted to the geminal-dimethyl group at C-2 in the cyclopropane ring, with very interesting stereospecificity [Eq. (9)] (*43*). The 1R,3S isomer is hydroxylated by rat and mouse mfo systems only at the 2-*cis*-methyl while the 1S,3R isomer is oxidized exclusively at the 2-*trans*-methyl group. In the 1R,3R isomer, rat microsomes preferentially hydroxylate the 2-*trans*-methyl group while mouse microsomes do so at the 2-*cis*-methyl position. [1S,3S]-Permethrin is mostly hydroxylated at the methyl *cis* to the carboxyl by rat and *trans* by mouse microsomes. The preferred methyl group for hydroxylation varies not only with the isomer but also with the species from which the microsomal preparations are obtained.



(9)

Toxicology

The toxicology of pyrethroids with dihalovinyl substituents is similar to that of the pyrethrins and other pyrethroids. Permethrin has been studied in greater detail (*45, 46*) than other dihalovinyl pyrethroids, but unpublished studies by several laboratories on NRDC 149 and decamethrin indicate that they have many of the same characteristics.

Table 3. Systems in which permethrin shows no mutagenic activity.

Method	Species	Strain	Permethrin amount	Metabolic activation system	Positive control and amount	Ref.
Bacterial assays, reversion of tryptophan requirement	*Escherichia coli*	W3623*trp*A; W3102*trp*E	10,000[a,b]	No	*N*-Methyl-*N'*-nitro-N-nitrosoguanidine (100); 4-nitroquinoline *N*-oxide (*10*)[a]	(*45*)
		WP2	1–1000[a,c]	Yes	*N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine (2)[a]	[d]
Bacterial assays, reversion of histidine requirement	*Salmonella typhimurium*	TA1535; TA1538	10,000[a,b]	No	*N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine (100); 4-nitroquinoline *N*-oxide (10)[a]	(*45*)
		TA1535	1–1000[a,c]	Yes	*N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine (2)[a]	[d]
		TA1537	1–1000[a,c]	Yes	9-Aminoacridine (100)[a]	[d]
		TA1538, TA98	1–1000[a,c]	Yes	4-*o*-Tolylazo-*o*-toluidine (25)[a]	[d]
		TA100	1–1000[a,c]	Yes	Benzo(α)pyrene (20)[a]	[d]
Bacterial assays, inhibition zone of DNA-repair deficient mutant as compared with wild strain	*E. coli*	W3623 (wild); W3623*pol*A; W3623*uvr*A; W3623*rec*A	10,000[a,b]	No	*N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine (100) (100)[a]	(*45*)
	S. typhimurium	TA1978 (wild); TA1538*uvr*B	10,000[a,b]	No	(100)[a]	(*45*)
	Bacillus subtilis	H17 (wild); M45*rec*A	10,000[a,b]	No	Streptozotocin (20)[e]	(*45*)
Host-mediated bacterial assays, reversion of bacterial histidine requirement	*S. typhimurium* -mouse	G46	600 and 3000 (1R, 3S)[e] 21 and 54 (1R,3R)[e]		Ethylmethane sulfonate (620)[e]	[g]
Cultured lymphomal cells	Mouse	L5178Y/TK+/−	30–125[c,f]	No	2-Acetylaminofluorene (50)[e]	[g]
		L5178Y/TK+/−	16–94[c,f]	Yes	Trimethylphosphate (679)[a]	[i]
Dominant lethal system	Mouse	Charles River CD1	452[e,h]			

[a]In μg/plate.
[b]Tests on racemic mixture and each individual isomer (1R,3S; 1R,3R; 1S,3R; 1S,3S)
[c]Tests on racemic mixture.
[d]Data of G. P. Schoenig (FMC Corporation), unpublished results.
[e]In mg/kg oral dose.
[f]In μg/ml.
[g]Data of D. Clive (Wellcome Research Laboratories), unpublished results.
[h]In mg/kg, 5 daily oral doses to male mice.
[i]Data of B. C. Chesher, J. C. Malone, and M. J. Parker (Wellcome Research Laboratories), unpublished results.

[1RS,3RS]-Permethrin has an acute oral LD_{50} of 490 mg/kg for male and female mice and >5000 mg/kg for male and female rats (*45*). Various laboratories and even the same laboratory (*46*) report the rat oral LD_{50} values of [1RS,3RS]-permethrin from ~ 450 to >5000 mg/kg, without explanation as to the possible reasons for the discrepancies. The individual isomers of permethrin have mouse oral LD_{50} values as follows: 1R,3S-3150 mg/kg; 1R,3R- ~96 mg/kg; 1S,3R and 1S,3S- >5000 mg/kg (*45*). The toxicity of isomer mixtures approximates that expected if there is no potentiating effect of one isomer component with another. The symptoms of permethrin poisoning in mice and rats include hypersensitivity, tremor and motor ataxia, sometimes with fibrillation and salivation. The subcutaneous and dermal toxicities are very low as compared with the oral toxicity. Permethrin does not cause eye or skin irritation or skin sensitizing effects. In six-month feeding studies with rats, the dietary no-effect level is 1500 ppm. At a higher level (3000 ppm) there is slight hypertrophy of hepatoparenchymal cells. The acute and subacute inhalation toxicity to rats and mice indicates a wide margin of safety between the no-effect concentration of permethrin and the levels likely to be used as aerosols in insect control.

Mutagenicity tests in a variety of systems give no indication that permethrin poses a problem in this respect (Table 3). The studies with bacteria include strains sensitive to base-pair substitution and frameshift mutagens, and with increased permeability to large molecules and DNA-repair deficient mechanisms. The bacterial tests were made with and without exogenous metabolic activation (mouse and rat liver homogenate) and also in a host (mouse)-mediated assay. Tests on mammals were made with cultured mouse lymphomal cells with and without metabolic activation and by the dominant lethal system in male mice. The doses tested varied from low to high levels. These findings are of particular interest because of the relatively high correlation between mutagenicity and oncogenicity and because permethrin bears a partial structural similarity to two chemical carcinogens, vinyl chloride (*47*) and 1,1-dichloro-2,2-bis (*p*-chlorophenyl) ethylene (*48*). It appears that the dichlorovinyl group as a portion of the permethrin molecule does not confer mutagenic activity under the test conditions used. Permethrin is not teratogenic in mice when administered orally from days 7 to 12 of gestation at doses of 15, 50, and 100 mg/kg (*45*).

Decamethrin has an acute oral LD_{50} of 67–139 mg/kg for male and female rats and 19–34 mg/kg for male and female mice, the range in values resulting from the use of different carrier solvents for administration (*49*).

Prior to extensive use of permethrin and related dihalovinyl-containing pyrethroids in pest control, further carcinogenicity and multigeneration reproduction tests must be completed.

The toxicity of some pyrethroids administered intraperitoneally to mice is increased by the mfo inhibitor PB and an esterase inhibitor (*S, S, S*-tributyl phosphorotrithioate or DEF, a cotton defoliant) (Table 1). [1RS,*trans*]-Permethrin, on the other hand, appears to be so efficiently metabolized by both oxidases and esterases that its toxicity is not synergized by these compounds. If synergists are to be used with dihalovinyl-containing pyrethroids, they must be selected with care and thoroughly tested to ascertain that no unique hazards are associated with such combinations.

Pyrethroids in general seem to have low toxicity to birds but very high toxicity to fish (*45*). They must be used under conditions that fish are not exposed directly or indirectly to avoid severe environmental consequences.

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